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10/688,794	10/15/2003	Kent Jardemark	58073 (47137)	9727

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EXAMINER	
KOSSON, ROSANNE	
ART UNIT	PAPER NUMBER
1652	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/688,794	JARDEMARK ET AL.	
	Examiner	Art Unit	
	ROSANNE KOSSON	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-62,64,65,67,71,79,81,83,85,87,89-91 and 103-106* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-62,64,65,67,71,79,81,83,85,87,89-91 and 103-106* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 January 2011* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' submission filed on January 28, 2011 has been received and entered. Claims 55, 57, 60, 90, 104 and 106 have been amended. Claims 1-54, 63, 66, 68-70, 72-78, 80, 82, 84, 86, 88 and 92-102 have been canceled. No claims have been added. Accordingly, claims 55-62, 64, 65, 67, 71, 79, 81, 83, 85, 87, 89-91 and 103-106 are examined on the merits herewith.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Drawings and Specification

New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because the drawings filed on April 10, 2010 are ambiguous. Applicants are advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance. This objection has been modified in accordance with the amended drawings.

As previously discussed, the new drawings are ambiguous, because one reference numeral, "5," for substrate, is used for several different kinds of structures. Each kind of structure should have a different label. Figs. 5 and 6 appear to have the same substrate (5). In Fig. 10A, substrate (5) is a microfluidics channel. In Fig. 10B, substrate (5) appears to be the base and lid of a measurement chamber in which a cell is mounted on a patch clamp electrode. In Fig. 11, substrate (5) is a "Chip substrate" into which a number of parallel grooves have been cut for conducting multiple liquid streams. In Figs. 13 and 14, substrate (5) appears to be a

rectangular plate into which a number of converging grooves lined with wells have been cut for conducting multiple liquid streams to a reservoir. As noted above, for clarity, each structure or device should have its own numerical label. For each corrected drawing, the Description of the Drawings should be amended accordingly. Appropriate correction is required.

Applicants have declined to amend the drawings, apart from Fig. 6. Amended Fig. 6 now makes it clear that part no. 3 refers to the nanoelectrode array. The substrates in Figs. 5 and 6, which have the structure of a plate or slide, are the same. Thus, Figs. 5 and 6 are acceptable. Applicants assert that they have not corrected the drawings, because correcting the drawings would redefine the term "substrate" and make it inconsistent with the specification and the prior art. Applicants cite 37 CFR 1.84(p)(4), which states that the same part of an invention must always have the same reference character when shown in different views.

In reply, this section of the CFR is not on point. This section means that if one device is shown in different views, e.g., from the top, from the bottom, from the front, from the back, etc., each piece of the device must have the same reference character in each drawing. Such is not Applicants' situation. Applicants may have misunderstood the objection. The different drawings show different devices, and the type of substrate in each device is different. A part no./ reference character should refer to one specific three-dimensional structure that is a piece of a device only. As Figs. 5 and 6 have the same type of substrate, each substrate may be labeled (5). Fig. 10(A) shows a two-piece plate-and-lid, device. Fig. 10(B) shows a different two-piece plate-and-lid device with electrodes built into the plate. Fig. 11 shows a microchip. Figs. 13 and 14 show a plate containing a pattern of reservoirs and channels. The different types of substrates in Figs. 10(A), 10(B), 11 and 13-14 represent four different types of parts of devices. Each of these four should be labeled with a different part no. that is not 5 and that has not already been used for another part. The specification should be amended accordingly.

Typically, different embodiments of a device, shown in different drawings, have different part nos., even for corresponding features, because their structures are different. Applicants have not explained how simply using different part nos. is inconsistent with the specification and the prior art. The objection of record is maintained.

Claim Rejections - 35 USC § 112, second paragraph

In view of Applicants' amendments to the claims, the rejections in the previous Office action have been modified to mirror the amended claims.

Claims 55-62, 64,65, 67, 71, 79, 81, 83, 85, 87, 89-91 and 103-106 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Portions of this rejection has been discussed in the previous Office actions.

To reiterate, claims 55 and 60 are confusing and ambiguous in their recitation of the claimed microfluidics system, and the structure of the claimed apparatus still cannot be understood, rendering the meaning of claims unclear. It is not clear how the tip is connected to the housing that defines the lumen. It is not clear how the housing defines the lumen and how the housing, the lumen and the aperture are put together. Is the aperture an opening into the lumen? Is the housing a hollow cylinder, the interior of which is the lumen? How are the tip and the housing put together with the measurement chamber and the substrate? The claims recite that the substrate has an outlet that is connected to the measurement chamber, and it has an inlet. But the inlet and outlet are not connected, and the inlet is not connected to anything. Also, the claims recite that the outlet delivers a solution into the measurement chamber. What then is the outlet an outlet of? An outlet should empty fluid from a chamber. What does the inlet do?

In claim 60, what is the structural arrangement of the plurality of electrodes and the measurement chamber? How are they put together? What is "the substrate of the walls?" Is only one tip raised from the substrate of the walls, or are all of them, the plurality, raised? Again, it is unclear what the structure of the substrate is. Clarification and appropriate correction are again required. As discussed in previous Office actions, Applicants may refer to a drawing and claim the device of Fig. N, N being a specific figure no.

Claim 71 is unclear, because of the amendments to claims 55 and 60. If the substrate is now a multi-well plate (or a solid support having at least one well), it is not clear how it is "interfaced" to a multi-well plate through an external tubing or capillary. This use of the term "interfaced" is not defined in the specification. The structure in this claim cannot be determined. Clarification and appropriate correction are required. Nevertheless, an interpretation is required to proceed with prosecution. The claim has been interpreted to mean that the substrate comprises a multi-well plate and that external tubing runs from the multi-well plate across a portion of the substrate.

Claim 90 recites that the scanning mechanism can move cells across microchannel outlets or it can move microchannel outlets relative to cells, or it can move a fluid stream across a cell. How is each of these three possible, and how is each of these three performed? A scanning mechanism that scans cells in a microtiter plate or on a microchip or in the channels or reservoirs of a plate is typically an optical scanner that can detect a particular feature of the cells, such as a detectable label or a cell size, by measuring fluorescence or luminescence or light emission or light scattering. The nature of the scanning mechanism, which can move things, is not clear. Regarding claim 106, this claim is clearer, because increasing the pressure or the flow rate for a fluid stream containing cells in a microchannel will move fluid across the cells. But, the claim is confusing, because the scanning mechanism is not related to moving the

fluid. The pressure and flow rate are controlled by a pump that moves fluid (cell culture medium) across that portion of the device. Clarification and appropriate correction are required. If Applicants can explain, based on the specification and the prior art, how a scanning mechanism can move things, the rejection will be reconsidered. Nevertheless, an interpretation is required to proceed with prosecution. Claim 90 has been interpreted to mean that the scanner can move over or across cells or microchannels or fluid in the device, to scan for something. Claim 106 has been interpreted to mean that the scanner can scan a cell as fluid moves over it, the fluid flow being controlled by pressure or flow rate in the microchannels.

In their Response, Applicants describe the amendments to the claims that now recite different features. But, as discussed above, the features are not connected to each other, such that the structure of the devices is still unclear and confusing. Regarding claim 90, Applicants assert that the scanning mechanism is not an imaging device. Applicants refer to specific portions of the specification to support the claim. Thus, the claim is not new matter. But, these portions of the specification are equally confusing and do not explain the claim. What is the scanning mechanism? Is it some sort of micron-scale robotic arm that moves cells within the device? Is the scanning mechanism the same thing as the micro-electrode (or patch clamp electrode) that contacts the cells and to which the cells adhere? If such is Applicants' current interpretation of the term, as discussed in the previous Office action, p. 7, first paragraph, of the specification discloses that the term scanning mechanism has its ordinary meaning in the art. It comprises a detector for detecting changes in the electrical properties of the cells. That is, it is connected to the electrodes. An interpretation is required to proceed with prosecution. As previously discussed, the term scanning mechanism is considered to have its conventional meaning. Thus, the amended claims do not overcome the rejections.

Claim Rejections - 35 USC § 103

In view of Applicants' amendments to the claims, the rejection in the previous Office action has been modified to mirror the amended claims.

Claims 55-62, 64, 65, 67, 71, 79, 81, 83, 85, 87, 89-91 and 103-106 remain rejected, under 35 U.S.C. 103(a) as being unpatentable over Maher et al. (US 2002/0025568 A1) and He et al. (US 2003/0049862 A1) in view of Peeters (US 6,123,819) and Hamill et al. ("Improved patch-clamp techniques for high-resolution current recording from cells and cell-free membrane patches," Pflügers Archiv 391:85-100, 1981). This rejection has been discussed in the previous Office actions.

To reiterate, Maher et al. disclose an apparatus for carrying out electrical measurements on cells. The apparatus comprises a substrate comprising an array of measurement chambers (a microtiter plate) that contain cells. The measurement chambers have walls surrounding a base. The apparatus comprises an array of microelectrodes that match the wells in the microtiter plate and that are arranged in a lid or cover. The electrodes may be solid (i.e., have solid tips) or fluid filled (patch clamp electrodes). Patch clamp electrodes have a tip, a housing that defines a lumen and an aperture, and they can be inserted into a cell membrane, which is a lipid-based cell structure. The tip has a contacting surface that has a diameter of about one micron, which is a value of less than about one micron, as "about one micron" includes values greater than and less than one micron. The electrode is filled with a conducting electrolyte solution (a buffered salt solution). See Figs. 1, 3 and 9 and paragraphs 11, 15, 127, 136, 137, 143, 144 and 160. See also Hamill et al., p. 86, second full paragraph and right col.; p. 91, left col.; p. 92, left col.; and Figs. 1, 2A, 6A, 9 and 10 on pp. 86, 87, 91, 93 and 94. The apparatus is part of a computer-controlled system that operates the electrical, mechanical and optical aspects of the apparatus, as it controls the activity of the electrodes, movement of the microtiter

plate, spectroscopic readings of the wells in the microtiter plate, and data collection and analysis. The electrodes are compatible with microfluidics equipment (see paragraphs 197, 198, 202 and 205-208). Maher et al. do not disclose that the measurement chambers have microchannels.

He et al. disclose a microfluidics system, in which the microfluidics plumbing is incorporated into the lid for a standard microtiter plate, thereby providing the measurement chambers with microchannels that are inlets and outlets. The outlets can deliver an aqueous solution to the measurement chambers from a reservoir of that fluid (continuous fluid delivery). See paragraphs 6-12 and 35-45. The measurement chambers are circular and the microchannels may be radially disposed with outlets in the chambers (see paragraph 39). The system comprises a pressure control device for controlling the positive and negative pressures to the microchannels, which fills and empties the measurement chambers, allowing assays to be performed and the chambers to be washed (see paragraph 49).

The claimed microfluidics system is the apparatus of Maher et al. in which the microtiter plate lid has been modified with the microfluidics plumbing of He et al. It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the microtiter plate of Maher et al. with the microfluidics plumbing for microtiter plate lids of He et al., because He et al. disclose that this modification transforms the apparatus into a high-throughput apparatus, using standard industry equipment, for carrying out the most common types of automated assays used in the biotechnology and pharmaceutical industries, biochemical and genomics assays. Microfluidics chips, by comparison, require specialized custom equipment and have much lower throughput, i.e., they perform far fewer assays in the same amount of time (see paragraphs 6-7) (see claims 55-62, 64, 65, 67, 91 and 103-105).

Regarding claim 71, in modifying the apparatus of Maher et al. with the microfluidics

plumbing of He et al., the plumbing (microchannel tubing) would have been inserted in the lid, which is a substrate that is attached to the measurement chambers (see Maher et al., Figs. 1A, 1B and 3; see He et al., paragraphs 43-44 and Figs. 3-4). As discussed previously and above, the structure of the claimed device is unclear, and the substrate may be one piece or two pieces joined together. The substrate comprising a microtiter plate with a lid closed on top of it is a substrate that comprises and is interfaced with a multi-well plate. External tubing runs into the multi-well plate and across other portions of the substrate. Thus, this claim does not define the invention over the prior art.

Regarding the computer-controlled equipment for manipulating the microfluidics system (claims 79, 81, 83, 87 and 89-91), as previously discussed, Peeters discloses a microfluidics system comprising a nanoelectrode array on a substrate in a measuring chamber that holds fluids. The array and the chamber are connected to a microfluidics system for the delivery and removal of materials to and from the array via microchannels. The array is connected to a microcontroller or microprocessor, which analyzes signals from the microelectrodes and controls the microfluidics system. The pressure in the microchannels is controlled by an external micro-pump (see Figs. 1-3 and 5; col. 3, lines 21-35; and col. 8, line 38, to col. 9, line 7). Scanning of the nanoelectrode array in the x-y plane at specific positions is computer-controlled and very precise, similar to scanning a DNA chip, and scanning may be performed with a laser. Thus, the laser can scan a cell structure such as protein on the array relative to a microchannel outlet when the chip array of Figs. 1-3 is used in one of the chambers in Fig. 5. Signals from the electrodes can be amplified via transistors. See col. 10, lines 20-30; and col. 10, line 41, to col. 11, line 6). It would have been obvious to one of ordinary skill in the art at the time of the invention to use the computer-controlled equipment of Peeters with the apparatus of Maher et al. (modified with the plumbing of He et al.), because, as noted above, Maher et al.

disclose that their apparatus is designed for use with computer-controlled equipment. Peeters discloses the same computer-controlled equipment but is more explicit about the specific tasks and operations that the equipment performs.

Regarding claim 85, as previously discussed, Peeters does not disclose that the operation of the scanning mechanism (e.g., the rate, direction or number of repetitions of scanning) is responsive to a signal from the detector. But, it would have been obvious to one of ordinary skill in the art at the time of the invention that, if an electrode or a portion of an electrode array, during an experiment, showed one or more regions of interest (e.g., particularly high or low amounts of bound molecules or cell fragments), the software controlling the scanner would have been manipulated to scan in greater detail those regions of interest. Those regions of interest would have been scanned at a different speed to obtain better resolution, and multiple scans would have been performed. Therefore, this claim does not distinguish the claimed invention over the prior art.

Regarding claim 90, as discussed above, the claim appears to mean that the cells in the microchannel outlets (somewhere in the wells) or in the fluid streams (as fluids are pumped into and out of the wells) are scanned by a scanning mechanism. The claim appears to mean that imaging or some type of biochemical information for the cells is retained as the microchannels or the cells in them are scanned. A scanner can scan the cells, but it cannot move them. The laser scanner and the imaging equipment would have been readily programmed by one of ordinary skill in the art at the time of the invention to detect one or more cells at any desired location within a measurement chamber or within a microchannel and to scan the entirety of the measurement chambers and the microchannels (i.e., the entire microtiter plate). Therefore, this claim does not distinguish the claimed invention over the prior art.

Regarding claim 106, as discussed above, controlling the pressure and flow rate in the

microchannels is part of operating a microfluidics system, including the claimed microfluidics system. The scanner can be moved to scan a cell in any measurement chamber of the device. This claim, therefore, does not distinguish the claimed invention over the prior art.

Applicants assert that the claimed invention is not obvious, because the cited references do not disclose a substrate comprising a single microfluidic structure or tips that are raised from the walls of the substrate or the base of the substrate. In reply, the microfluidic structure of the claims is a combination of a well with a microchannel outlet and an electrode that can contact a cell. The substrate has a microchannel inlet. The rest of the structure is nebulous and undefined. Because of the comprising language, the substrate can comprise multiple microfluidic structures and can be a microtiter or other multi-well plate. This structure is disclosed by the combination of Maher et al. and He et al. In this structure, the tips of the electrodes, in the top portion of the substrate, are raised from the base of the substrate. Consequently, this feature does not define the claims over the prior art.

Applicants assert that the claimed invention is not obvious, because their scanning mechanism moved cells across microchannels. It does not scan cells. It changes the position of the cells relative to the position of the microchannel outlets. In reply, as discussed above, this point is unclear, and the specification does not disclose how the scanner moves cells across microchannels. If Applicants can explain how the scanner accomplishes this movement, the rejection will be reconsidered.

In view of the foregoing, a holding of obviousness is again required.

No claim is allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this

Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROSANNE KOSSON whose telephone number is (571)272-2923. The examiner can normally be reached on Mon., Tues., Fri., 8:30-6:00, Thurs., 8:30-2:00, Wed. off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert B. Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Rosanne Kosson/
Examiner, Art Unit 1652
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